

Regulation, innovation and personalised medicine

The governance of pharmacogenomics in
Europe and the USA

Presentation at
EMA workshop, London, October 2012

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“The ratio of vision to data is very high ... We love vision, but data is our mainstay.”

**Jerry Collins, Director, Laboratory of
Clinical Pharmacology, FDA, 1998.**

“This first decade of the 21st century began with the decoding of the human genome—a scientific achievement that we knew had the potential to transform our understanding of health and disease and revolutionize our fundamental approach to medicine.”

Margaret Hamburg, FDA Commissioner, 2009

“The concept of personalised medicine is steadily evolving from a theoretical concept into an integral part of modern medicine.”

EMA Roadmap to 2015

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Phase one: information gathering – 2000-2004

- EMA and FDA convene conferences and workshops with industry and scientists
- Formation of working groups within FDA and EMA
- FDA meetings are co-chaired by industry, EMA participate
- Briefing meetings/voluntary genomic data submission (VGDS) process – industry share PGx data outside formal regulatory review system
- FDA create IPRG, EMA create PGWP
- FDA and EMA hold bilateral VGDS

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FDA Critical Path report 2004



EMA Road Map to 2010 2005



The European Medicines Agency

London, 4 March 2005
Doc. Ref: EMEA/H/34163/03/Final

The European Medicines Agency Road Map to 2010:
Preparing the Ground for the Future

“A new product development toolkit — containing powerful new scientific and technical methods such as ... biomarkers for safety and effectiveness, and new clinical evaluation techniques — is urgently needed to improve predictability and efficiency along the critical path from laboratory concept to commercial product.”

FDA Critical Path Report

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Phase two: standard-setting

- Collaboration between regulatory, industry and academic scientists in new *pre-competitive* space
 - Critical Path Institute
 - Innovative Medicines Initiative
- Bilateral EMA/FDA cooperation - validating genomic data for use in regulatory decision-making e.g. Predictive Safety Testing Consortium

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Phase three: implementation

FDA's relabeling project

“At the beginning of the decade, the FDA began looking for opportunities to improve the quality of therapeutics using already marketed drugs by updating the labels to include PGx information.”

Lesko and Zineh, *Pharmacogenomics*, 2010

Warfarin pharmacogenetics : poster child or problem child?

“Patients carrying one or two variant CYP2C9 alleles had a higher incidence of supratherapeutic INR values (> 4), required a longer time to achieve stable dosing and reported a higher rate of serious or life-threatening bleeding events during initiation of warfarin therapy.”

“All these data are so convincing that drug therapy with warfarin is most likely to be the first example of CYP2C9 genotyping in clinical practice.”

“... before routine genotype-guided dosing recommendations can be made for patients, future studies ... need to be completed, especially prospective studies evaluating such genotype-guided dosing strategies.”

Kirchheiner et al (2004) *Personalised Medicine*

Warfarin pharmacogenetics : poster child or problem child?

- 2005 - FDA clinical pharmacology advisory committee vote 8-2 for relabeling of warfarin
 - 2006 - Critical Path Opportunities List
 - Priority one: biomarker development e.g. warfarin – need for PGx-based “rigorous dosing protocols”
 - 2007 - FDA relabel warfarin (no dosage guidance)
 - 2007 - CoumaGen study (CPI-funded)
- “ ... pharmacogenetic + clinical factors = initial dose more closely predictive of the stable maintenance dose ... fewer and smaller dose adjustments ... fewer INR measurements.”

BUT “ ... the study failed to achieve its primary end point of a reduction in out-of-range INRs.” **Anderson et al Circulation 2007**

Warfarin pharmacogenetics : poster child or problem child?

- 2008 - rejected by professional bodies and payors
 - American College of Chest Physicians, American College of Medical Genetics, Blue Cross Blue Shield
- 2008 - CMS public consultation on coverage
- 2009 - CMS decision: more outcomes data needed from RCTs
 - coverage with evidence development
- 2010 - FDA relabel again with PGx-based dosage guidance based on Medco/Mayo study (prospective observational)
- Clinical uptake still limited

What can we learn from Warfarin?

The complexity of the postmarket regulatory space

- Multiple gatekeepers
 - Health Technology Assessment agencies
 - Healthcare payors
 - Professional bodies
- Varying degrees of commitment to personalised medicine amongst different gatekeepers
- Regulatory agencies' authority is greater in premarket regulatory space

What can we learn from Warfarin?

- What were the areas of agreement?
 - Improving safety of warfarin dosing desirable
 - PGx plays role in inter-individual variation in drug response
 - More data on warfarin PGx desirable
- What were the areas of disagreement?
 - The value of different types of evidence
 - Molecular mechanism+observational data vs. RCTs
 - Personalised Medicine vs. Evidence-Based Medicine

What can we learn from Warfarin?

RCTs – not fit for purpose?

“...although population-based, randomized, controlled trials of drugs control for disease variability, they generally do not reveal why some people do not have a response to treatment, others have excessive pharmacologic responses, and still others have side effects that occur in a distinctive pattern for a given drug.”

Lesko and Woodcock, NEJM, 2009

“Most development programs must rely on *trial and error* empirical testing, rather than on more mechanistic approaches built on new molecular and genomic knowledge.”

Lester Crawford, Acting FDA Commissioner,
Critical Path Opportunities Report, 2006

What can we learn from Warfarin?

RCTs – still the gold standard?

Evidence-Based Medicine operates with an epistemology which is “overwhelmingly empiricist and grounded in epidemiological and statistical reasoning.”

It is interested in what works, and what works best; “How the intervention works, physiologically ... is less relevant.”

Timmermans and Berg (2003) *The Gold Standard*.

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EMA's attitude to relabelling

“From the regulatory point of view, the associations highlighted above will need to be robust and validated. Observational studies /data or association studies alone may not be adequate to provide a basis for a regulatory action such as inclusion of PG information in the product literature (SPC/label).”

(EMA, 2008)

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EMA's authority to relabel

“... matters concerning medicinal products approved nationally are discussed at the level of the National Competent Authorities in the member states..”

(EMA 2008)

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EMA's authority over companion diagnostics

“The legal requirements for In Vitro Diagnostics (IVDs) or other medical devices are outside the scope of this paper and are addressed in other relevant legislation and guidelines.”

(EMA 2010)

European Commission's consultation on future of medical device regulations raised possibility of role for EMA. Some support for this proposal but also much opposition.

No role for EMA in EC's new IVD regulation.

IVD regulation and PGx

Gaps in IVD device regulations

- **European Union**
 - Nearly all tests are classed as low-risk, so are not subject to independent pre-market review
 - Lack of clarity on need for evidence about clinical validity of tests
 - Ambiguity of status of Laboratory Developed Tests (LDTs)
- **USA** : Ambiguity of status of Laboratory Developed Tests (LDTs)

IVD regulation and PGx

Development in IVD device regulations

Sep 2012 - European Commission issues proposal for new regulation

- New risk classification – genetic tests and companion diagnostics subject to pre-market scrutiny by NBs
 - Clarifies need for evidence about clinical validity
 - Clarifies status of Laboratory Developed Tests (LDTs)?
 - Definition of companion diagnostic
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- **USA** : Ambiguity of status of Laboratory Developed Tests (LDTs)

IVD regulation and PGx

Development in IVD device regulations

USA

- 2007 - FDA issues IVDMIA draft guidance
- 2008 - SACGHS report recommends FDA action
- 2010 - FDA holds public meeting on LDT regulation
- FDA LDT draft guidance ???
- Meanwhile some LDTs have gained FDA approval e.g. Agendia Mammaprint

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Conclusions

- Creation of new socio-technical spaces
 - pre-regulatory, pre-competitive, transnational
- Transnational cooperation fuelled by (and reinforcing) the existing dynamic of harmonisation/cooperation within EU and globally
- Differences in implementation (arising from different evidence standards and legal powers)
- No transnational harmonisation on device side of PGx (e.g. different definitions of companion Dx)

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Next steps

- Greater coordination between FDA/EMA and HTA agencies?
 - a role for early HTA?
- EMA authority over companion diagnostics
 - Combination product route?
- FDA authority over LDTs
 - a post-election issue?
- From voluntary to mandatory submission?

Thanks for listening

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